Dose Regimen Optimization of PD-L1 Inhibitor and Nab-paclitaxel in Patients with NSCLC: a Quantitative Systems Pharmacology analysis

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Abstract

Introduction: Combining immune checkpoint inhibitor and chemotherapies provides more benefits than traditional treatment options in patients with NSCLC. However, some patients still have no clinical benefits. Clinical accessible biomarkers are necessary to predict clinical outcomes and optimize dose strategies. The study aimed to investigate accessible biomarkers that can predict clinical outcomes and optimize dosing strategies of atezolizumab and nab-paclitaxel combination therapy in patients with NSCLC by quantitative systems pharmacology (QSP).

Methods: The model was developed based on a published QSP model of triple-negative breast cancer using the SimBiology toolbox in MATLAB. The model included four compartments. With the model, we generated a virtual patient cohort to conduct in silico virtual clinical trials and used available data from real clinical trials (IMpower131) for model calibration and validation.

Results: The final QSP model predictions are consistent with clinically reported efficacy endpoints. CD8+ and CD4+ T cell densities in tumor are significantly affected by the response status. Roc analysis further implicating their potential to be predictive biomarkers for this double combination regimen. Virtual clinical trial simulation shows reduced nab-paclitaxel doses from 100 mg/m2 to 75 mg/m2 would leads to lower ORR but was higher than atezolizumab monotherapy. Three atezolizumab dosing strategies combined with nab-paclitaxel showed comparable efficacy. to compare different schedules of the two drugs for simulated therapeutic optimization.

Conclusion: This study provides a QSP model, which can be used to generate virtual patient cohorts and conduct virtual clinical trials. Our findings demonstrate its

potential for making efficacy predictions for immunotherapies and chemotherapies, identifying predictive biomarkers, and guiding future clinical trial designs.
Keywords: quantitative systems pharmacology; atezolizumab; nab-paclitaxel; dosing regimen; non-small cell lung cancer

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1. Introduction

Lung cancer is the most common cause of cancer death worldwide, approximately 85% ； of patients have a group of histological subtypes collectively known as non-small cell lung cancer (NSCLC)[1]. Although chemotherapy and targeted therapy has been proven effective, the overall cure and survival rates for NSCLC remain low in the PD-L1–low subgroup. The introduction of immune checkpoint inhibitors (ICIs) such as monoclonal antibodies that target cytotoxic T-lymphocyte antigen-4 (CTLA-4) and antibodies against PD-1 or PD-L1 have signaled a new approach for lung cancer care.

Atezolizumab is an engineered, humanized monoclonal anti-PD-L1 antibody. Atezolizumab monotherapy was approved for the treatment of patients with locally advanced or metastatic non-small-cell lung cancer who were previously treated with chemotherapy by FDA (Food and Drug Administration) in 2019. Whereas response rates for patients with NSCLC ranged from 14% to 38% with single-agent atezolizumab, the IMpassion131 trial reported a response rate of 49.7% with the combination of atezolizumab and nab-paclitaxel[2-4].

Nab-paclitaxel is a nanoparticle albumin-bound form of paclitaxel that does not require steroid premedication, which has potentially immunosuppressive effects. In IMpower131 study, Atezolizumab was administered at 1200 mg intravenously (IV; day 1) and nab-paclitaxel at 100 mg/m2 IV (days 1, 8, and 15). This combination was supported by the following rationale: nab-paclitaxel exhibit positive immunomodulatory effects by releasing high levels of tumor antigens and reinstating immunosurveillance, and atezolizumab reverses T cell suppression by selectively blocking interactions between PD-L1 and programmed death 1 (PD-1) on ICs and cancer cells[4];

According to the IMpower131 study (NCT02367794)[4], compared with nab-paclitaxel monotherapy, nab-paclitaxel plus atezolizumab significantly improved the progression-free survival (PFS), but did not prolong overall survival (OS) in the PD-L1–low subgroup. And further analyses are required to investigate the biomarkers in the PD-L1–low subgroup.

Quantitative systems pharmacology (QSP) is a mechanistic modeling approach that is used for the assessment of therapeutic intervention on a disease by linking descriptions of the molecular and cellular mechanisms of the disease and drug to

system-wide dynamics, bridging biomarkers and clinical endpoints relevant for the disease[5]. Wang et al[6] present a modular QSP platform for immuno-oncology that incorporates detailed mechanisms of immune–cancer cell interactions to make efficacy predictions and identify predictive biomarkers for treatments using atezolizumab and nab-paclitaxel patients with TNBC (Triple-negative breast cancer).

The study aimed to investigate accessible biomarkers that can predict clinical outcomes and optimize dosing strategies of atezolizumab and nab-paclitaxel combination therapy in patients with NSCLC by quantitative systems pharmacology (QSP).

2. Method

2.1 Model Development

2.1.1 Model Structure

The model structure was developed basing on a published QSP model of triple-negative breast cancer using the SimBiology toolbox in MATLAB (MathWorks, Natick, Massachusetts, USA), which comprises four compartments: central, peripheral, tumor, and TDLNs. The model was introduced with nine modules that describe the kinetics and dynamics of cancer cells, APCs, tumor-specific neoantigens and tumor-associated self-antigens, effector T cells (Teff), regulatory T cells (Treg), immune checkpoints, myeloid-derived suppressor cells (MDSCs), immunotherapeutic agents and chemotherapeutic drugs. In this study, we assume that the dynamics of the major species in the model are similar between patients with NSCLC and patients with TNBC (figure 1).

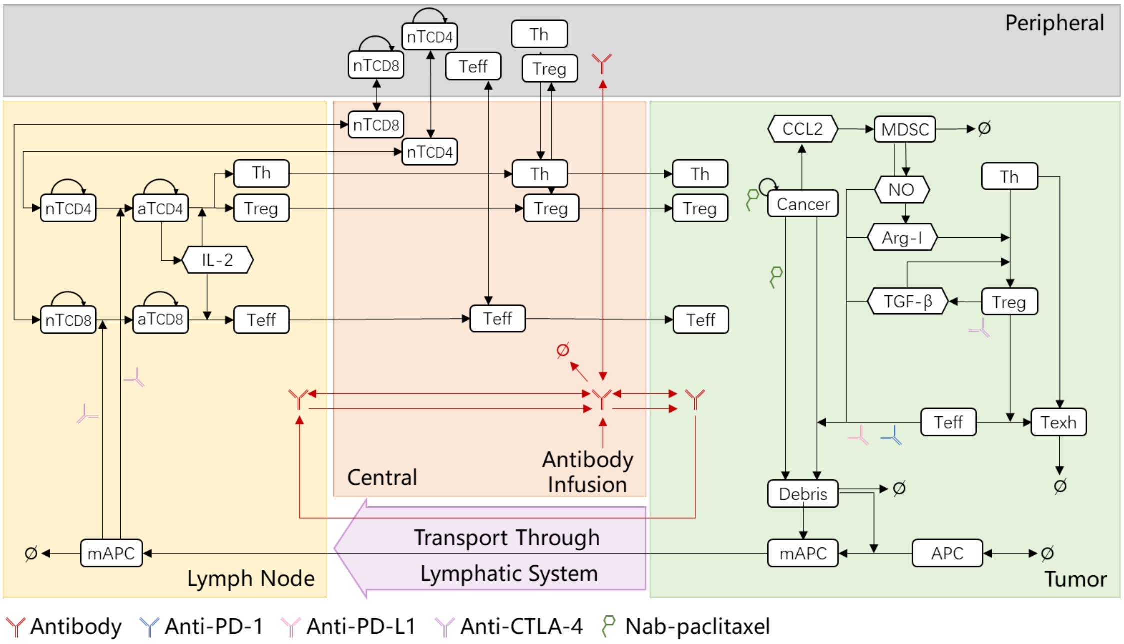

Figure 1. The dynamics of the major species in the QSP model of patients with NSCLC. The model is composed of four compartments: central, peripheral, tumor, and tumor-draining lymph node, which describe cycles of immune activation in lymph nodes, T cell trafficking to the tumor, killing of cancer cells, immune evasion, and antigen release and lymphatic transport. ARG-I, arginase I; AT, activated T cell; MAPC, mature antigen presenting cell; NO, nitric oxide; QSP, quantitative systems pharmacology; NT, naïve T cell; TEFF, effector T cell; TH, T helper cell; Treg, regulatory T cell.

2.1.2 Model parameters and validation

Parameter sensitivity analysis (PSA) was conducted to determine which parameters have a high impact on the variables of interest (tumor volume in our study) to capture the interindividual variabilities in patients. The initial values of model parameters of

NSCLC were based on clinical and experimental evidence from literature. Twenty-six parameters were investigated in PSA and were randomly generated using Latin Hypercube Sampling (LHS),. The sample size was 1000 and the selected input parameters are listed in supplemental tables S7. Partial rank correlation coefficient (PRCC) analysis was performed to identify the most influential factors.

Data from clinical trials were employed to further calibrate the distribution of the model parameters. Specifically, the published clinical results from the placebo comparator arm of the IMpower131 trial are used for model calibration, and the results from the intervention arm of the IMpower131 trial are used for model validation.

The total number of 1000 virtual patients are generated using LHS methods for efficacy predictions and statistical analyses. The major clinical outcomes were objective response rate (ORR) and duration of response (DOR) which were predicted based on RECIST V.1.1 and the 2.5th to 97.5th percentile of bootstrap are calculated for comparison between model predictions and clinical results.

2.2 Model application

2.2.1 Identification of Potential Predictive Biomarkers

After the model validation, subgroup analysis was used to identify potential predictive biomarkers. In subgroup analysis, 95% CI are estimated for the ORR predictions based on the normal approximation for the binomial distribution. For comparison of model observations in subgroups of different response status and treatment regimens, the Wilcoxon test is performed using ggpubr package in Rstudio V.1.2.

The performance of the predictive biomarkers identified previously is investigated using a binary classification model. The sensitivity and specificity values from each cut-off were plotted as receiver operating characteristic (ROC) curves.

2.2.2 Optimization of nab-paclitaxel and atezolizumab therapy

A series of virtual clinical trials are simulated using various doses and schedules of nab-paclitaxel and atezolizumab. Specifically, 840 mg every 2 weeks, 1200 mg every 3 weeks and 1680 mg every 4 weeks atezolizumab is administered on reaching the initial tumor diameter, in combination with nab-paclitaxel, and 50 mg/m2, 75 mg/m2, or 100 mg/m2 (on days 1, 8, and 15 of a 28-day cycle) of nab-paclitaxel is administered. Virtual cohort of 1000 patients with various dose regimens were created by LHS method. The median tumor volume and CD8+ T cell level in the tumor at week 8 are reported with the ORR for each combination of the treatment regimens.

3. Results

3.1 Model Development

3.1.1 Model Structure

The modified QSP model comprises 271 parameters, 215 ODEs, and 54 algebraic equations in total. The list of model parameters, reactions, algebraic equations, and cellular and molecular species are presented in supplemental tables S1-S6.

We optimized the rule of cancer cell capacity by using tumor diameter and spherical calculation formulas.

$$Cell_{max} = \frac{3}{4} \times \pi \times (\frac{DIA_{T,max}}{2})^3 \times DEN_{T,cell}$$

Where $Cell_{max}$, $DIA_{T,max}$ and $DEN_{T,cell}$ represent maximal cancer capacity, maximum tumor diameter and cancer cell density;

3.1.2 Model parameters and validation

The contribution of primary model parameters to the changes in the tumor size is investigated using parameter sensitivity analysis. Supplemental tables S7 lists a set of 26 parameters' distribution of the model in which they are varied for sensitivity analysis. Among the model parameters, tumor-specific T cell clone, rate of cancer cell death by Teff and max clearance rate from V1 compartment for nab-paclitaxel were the top parameters that correlated with the smaller tumor diameters (Figure.2). Conversely, tumor growth rate, rate of Teff inhibition by Treg and half-max concentrations of nab-paclitaxel for cancer killing are correlated with percentage increase in tumor size (Figure.2).

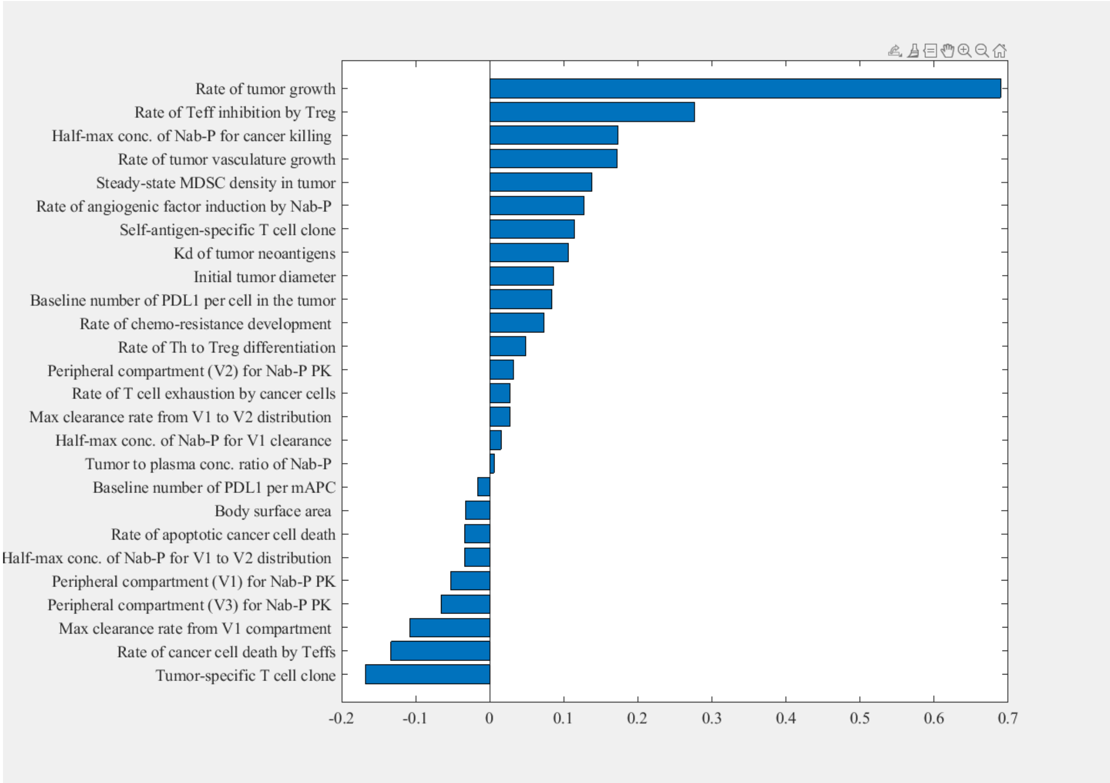

Figure 2. Parameter sensitivity analysis.

Sensitivity analysis was performed by varying a set of 26 parameters simultaneously and performing partial correlation analysis to find out the effect of those inputs on the model outputs, primarily percent change in the tumor size.

To match the clinical settings, the simulation time is set to be 750 days, which corresponds approximately to the median follow-up time of 24.8 months in the IMpower131 trial. Additionally, the simulated tumor diameters are recorded every 8 weeks, which corresponds to the frequency of tumor measurements in the clinical trial.

The model-predicted ORR and DOR are consistent with the clinical results, which fall within the 95% confidence interval of clinical data (**Table 1**).

Table 1. Efficacy prediction for the virtual patient cohort generated based on calibrated parameter distribution

	Nab-paclitaxel monotherapy		**Atezolizumab & nab-paclitaxel**	
	Predicted	Clinical (95% CI)	Predicted	Clinical (95% CI)
ORR, %	37	41.0 (35.7-46.6)	52.0	49.7 (44.3-55.1)
Median DOR (month)	5.6	5.2 (4.4-5.6)	7.47	7.3 (6.8-9.5)

3.2 Model application

3.2.1 Identification of potential predictive biomarkers

As shown in figure 3, the distributions of potential predictive biomarkers show different trends in the three treatment regimens.

Baseline CD8+ and CD4+ T cell densities in tumor have higher areas under curves (AUCs) (0.718 and 0.714, respectively) than Treg cell density and PD-L1 expression (0.661 and 0.564, respectively), implicating their potential to be predictive biomarkers for combination regimen (Figure 4).

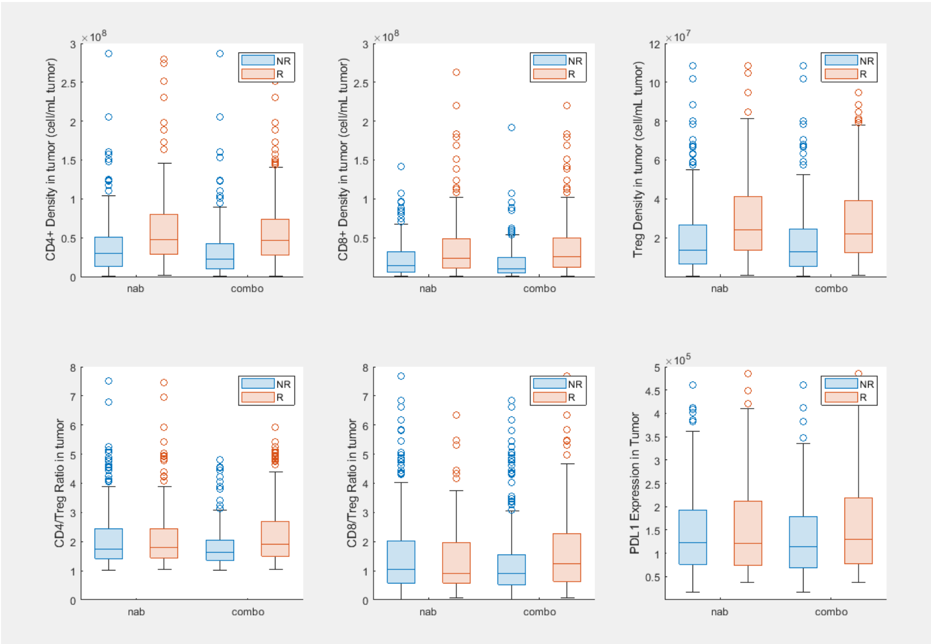

Figure 3. Pretreatment distributions of potential predictive biomarkers in responders and non-responders. Statistical significance is calculated by Wilcoxon test. Atezo, atezolizumab monotherapy 1200 mg every 3 weeks; Combo, atezolizumab 1200 mg every 3 weeks + nab-paclitaxel 100 mg/m2 Q3/4W; Nab-P, nab-paclitaxel 100 mg/m2 Q3/4W; NR, non-responders; R, responders.

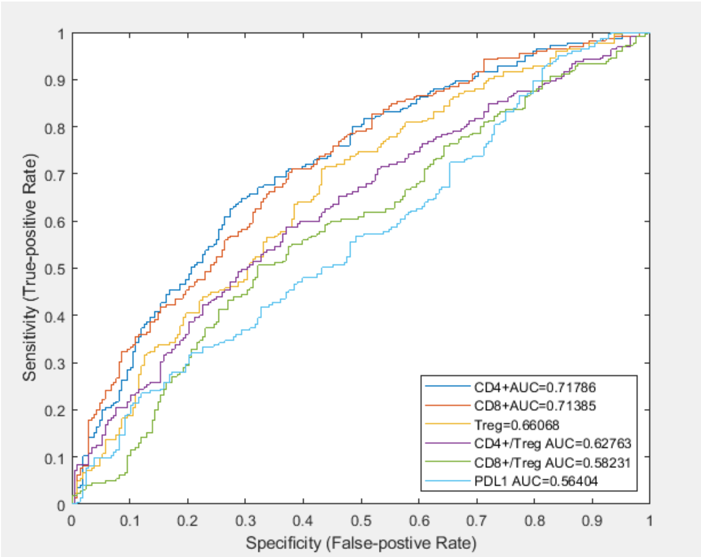

Figure 4. ROC analysis of potential predictive biomarkers in combination therapy. Cut-off values are selected based on the range of PD-L1 molecules on APCS, pretreatment effector T cell density, tumor mutational burden, and Teff to regulatory T cell ratio. For each cut-off value, response status (R vs NR) is predicted for each virtual patient by comparing the pretreatment amount of the potential predictive biomarker to the cut-off value. Sensitivity (true positive rate) is plotted against 1 – specificity (true negative rate) for each biomarker. APCs, antigen-presenting cells; AUC, areas under curve; NR, non-responders; R, responders; ROC, receiver operating characteristic.

3.2.2 Optimization of nab-paclitaxel and atezolizumab therapy

Model simulation results of ORR for different dosing regimens of various doses and schedules are shown in figure 4. 100 mg/m2 nab-paclitaxel combined with atezolizumab results in the highest predicted ORR in the concurrent therapy. 75 mg/m2 nab-paclitaxel combined with atezolizumab leads to higher ORR to nab-paclitaxel monotherapy. Three atezolizumab dosing strategies combined with nab-paclitaxel showed similar efficacy.

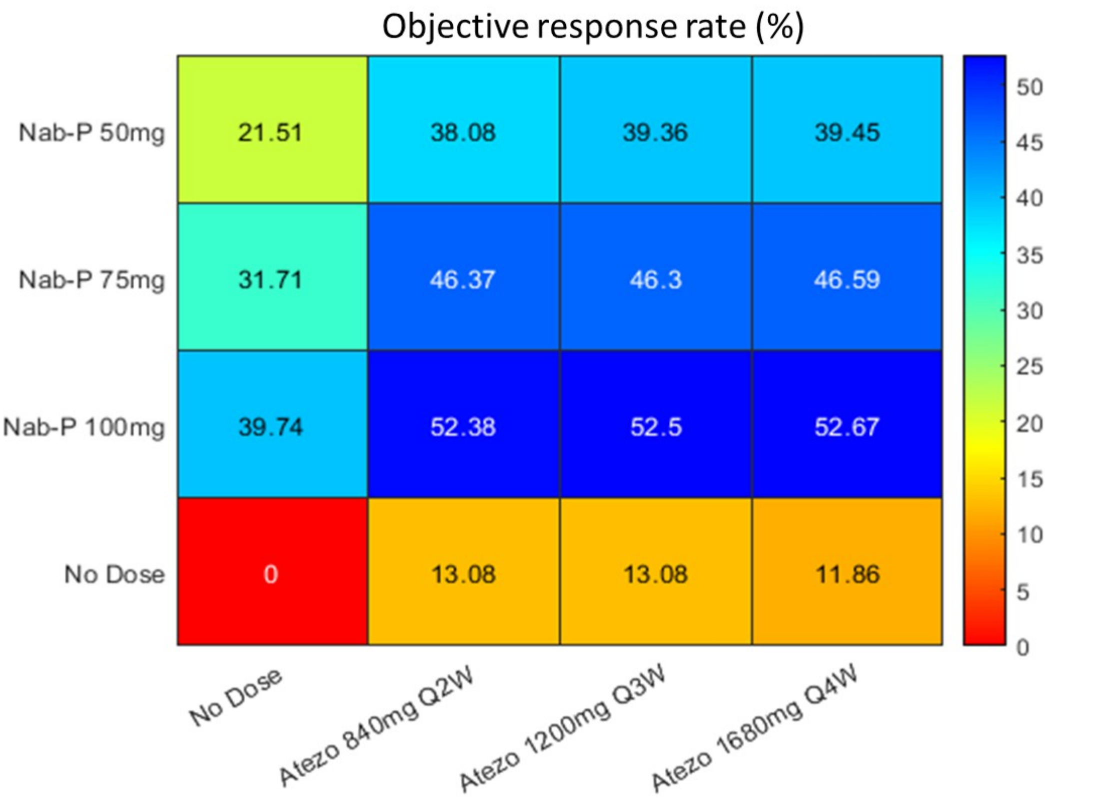

Figure 5. Model simulation results of ORR for different dosing regimens of various doses and schedules. Atezolizumab is administered 0, 840 mg every 2 weeks, 1200 mg every 3 weeks and 1680 mg every 4 weeks, in combination with nab-paclitaxel. And 50 mg/m², 75 mg/m² or 100 mg/m² nab-paclitaxel is administered staring on day 1, 8, and 15 of a 28-day cycle.

4. Discussion

In this study, we modified previously developed QSP platform of TNBC to NSCLC which means the process of anti-tumor immunity is similar between TNBC and NSCLC. In our model, effects of nab-paclitaxel included its cytotoxic, angiogenic, and antiangiogenic activities, which are reported by in vivo preclinical and clinical observations. As we incorporate all the mechanisms of action into the model, we can investigate the overall effect of nab-paclitaxel on tumor dynamics. The QSP model integrates laboratory data and clinical data, which allows us to better predict the dynamics of nab-paclitaxel and how it is associated with the response to the combination therapy.

In the biomarker analysis, the model first confirms that T cell densities in the tumor are associated with response status in PD-L1 antibody combined with nab-paclitaxel therapies. Besides, the model identifies that CD8+ and CD4+ T cell levels are the best two predictive biomarkers due to their significantly higher medians in responders and the significantly higher ORR in subgroups with high levels of T cells. The correlation between CD4+and CD8+T cell densities and drug response has been widely observed in single-agent PD-L1 blockade therapies. According to the distribution of cytotoxic immune cells in tumor microenvironment, tumors are classified into cold tumors and hot tumors. Cold tumors (low infiltration density of T cells) are prone to immune escape, resulting in poor efficacy of ICI monotherapy. But the relationship between CD8+T cell densities and response status in combination therapies Shall be further studied.

Furthermore, the combination of ICI and chemotherapy drugs increases the therapeutic effect of single drug treatment. We performed a series of in silico clinical trials to investigate the optimal dose schedule of atezolizumab and nab-paclitaxel for NSCLC. The results suggest that the reduction of nab-paclitaxel doses from 100 mg/m2 to 75 mg/m2 would lead~~s~~ to lower ORR but the efficacy was still higher than atezolizumab monotherapy. Three atezolizumab dosing strategies combined with nab-paclitaxel showed comparable efficacy. Optimal dosing strategies can be drawn according to the clinical conditions of ~~the~~ patient.

In this retrospective clinical trial analysis using our proposed QSP platform, we demonstrate its potential for making efficacy predictions of checkpoint inhibitors and chemotherapeutic agents by conducting virtual clinical trials. However, due to the complexity of immune system, our model has been simplified in terms of molecular and cellular mechanisms. And model simulations cannot entirely capture or reproduce the immune system and the clinical settings. In fact, the characterization of response status is also impacted by other conditions, such as patients' survival, new metastatic lesions, the definition of tumor burden as the sum of largest diameters, and resolution of the imaging modalities, all of which are likely to cause a deviation from model predictions.

5. Conclusion

The QSP model in patients with NSCLC reproduced clinical trial outcomes and showed good consistency with previous studies. ROC analysis implicated that baseline tumor CD8+ and CD4+ T cell densities were related to tumor response and could be utilized for predictive biomarkers. Reduced nab-paclitaxel doses from 100 mg/m^2 to 75 mg/m^2 would lead~~s~~ to lower ORR but was higher than atezolizumab monotherapy. Three atezolizumab dosing strategies combined with nab-paclitaxel showed comparable efficacy. Optimal dosing strategies can be selected according to the clinical conditions of the patient.

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Competing interests

The authors declare no competing interests.

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